UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/671,715	09/29/2003	Harry A. Dugger III	N9810.0025/P025	9275

24998 7590 01/14/2008
DICKSTEIN SHAPIRO LLP
1825 EYE STREET NW
Washington, DC 20006-5403

EXAMINER	
HAGHIGHATIAN, MINA	

ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
01/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/671,715	DUGGER ET AL.	
	Examiner	Art Unit	
	Mina Haghighatian	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10,22-26,28,40-46,48,57,59 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,22-26,28,40-46,48,57,59 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/30/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/30/07 has been entered.

Receipt is acknowledged of Amendments, Remarks, an IDS and a Declaration filed on 10/30/07. Claims 1, 22, 40 and 41 have been amended, while no claims have been canceled or newly added. Accordingly claims **1-8, 10, 22-26, 28, 40-46, 48, 57-59 and 61** remain pending.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-8, 10, 22-26, 28, 40-46, 48, 57-59 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deihl (WO 9413280) in view of Swaminathan et al (WO 9733621) and further in view of Physician's Desk Reference.

Deihl teaches a **sprayable analgesic** composition comprising an analgesic compound which is absorbed into the bloodstream through the **buccal mucosa** and a pharmacologically acceptable liquid carrier. In a preferred embodiment the active agent is ibuprofen and the liquid

carrier is **aqueous ethanol** (see page 3). The formulation may also contain other ingredients such as surfactants, humectants, **flavoring agents**, etc (see page 4). The table in example I shows the concentration ranges of each ingredient (SD alcohol and distilled water add up to provide a concentration of about 55% polar solvent. The formulation also contains about 12% active agent and about 3% fruit juice as flavoring). Deihl fails to disclose other suitable active agents for the said formulation, or the use of other solvents including polyethylene glycol and non-polar solvent.

Swaminathan et al teaches pharmaceutical compositions comprising an unpleasant tasting drug. The said formulations comprise an active agent, an effective amount of a polyhydric alcohol based carrier, which is an acceptable solvent and includes a polyol or a polyhydric alcohol such as propylene glycol or glycerine (see page 3). The polyol or polyhydric alcohol component of the composition may be selected form the group consisting of propylene glycol, glycerol, ethyleneglycol, diethylene glycol, dipropylene glycol, diglycerol, ethylene oxides, PEG 4000, PEG 6000, etc (see page 5). The formulations may also incorporate water in of up to about 40% by weight (page 6, lines 19-23). Other ingredients used in the said formulations include higher fatty acids, higher fatty acid esters, glycerine fatty acid esters, etc (see page 1).

Swaminathan also teaches that active agents may be selected from antacids, anti-inflammatory substances, analgesics, coronary dilators, diuretics, vasodilators, anti-infectives, stimulants, anti-histamines, decongestants, psychotropic, hypnotics, sedatives, anti-asthmatics, H2-receptor antagonist, etc. The examples of drugs include ibuprofen, ketoprofen, diclofenac, diltiazem, alprazolam, metoclopramide, erythromycin, azithromycin, etc (see page 3, line 28 to page 4, line 19).

Swaminathan et al also discloses that the said formulations may be in the form of a clear solution, dispersion or emulsion. A liquid formulation is preferred (see page 7).

Physicians' Desk Reference teaches the use of zolpidem, a hypnotic agent, for treating insomnia.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made given the general teachings of formulations for buccal mucosal administration of Diehl, to have looked in the art for other specific active agents and solvents suitable for spray formulations of liquid carriers, as taught by Swaminathan et al and Physician's Desk Reference, with reasonable expectations of successfully preparing suitable formulations for various therapies. Furthermore it would have been obvious to one of ordinary skill in the art to have substituted any suitable active agent for the analgesics of Diehl's buccal spray formulations as claimed. In other words, the claims would have been obvious because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Claims 1-8, 10, 22-26, 28, 40-46, 48, 57-59 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fu et al (WO 9303751) in view of Physicians' Desk Reference.

Fu teaches compositions and methods for the sublingual or buccal administration of therapeutic agents. The compositions comprise a therapeutic agent dissolved or dispersed in a

carrier which comprises a solvent, an optional cosolvent, and an oral mucosal membrane transport enhancing agent. The solvent comprises from about 50% w/v to about 95% w/v of the carrier of a non-toxic alcohol. Non-alcohols useful in the said formulations include ethanol, isopropanol, stearyl alcohol, propylene glycol, polyethylene glycol and the like. Most preferred alcohol is ethanol. The cosolvent is selected from water (page 4, lines 12-26). Essential or volatile oils such as peppermint oil, spearmint oil, menthol, etc, are added in a concentration of between about 1 and 5% w/v (page 5, lines 4-10). The said liquid compositions are formulated in a liquid spray or a liquid drop (page 6, lines 1-2). Fu et al lacks teachings on zolpidem.

Physicians' Desk Reference teaches the use of zolpidem, a hypnotic agent, for treating insomnia.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made given the general teachings of formulations for buccal mucosal administration of Fu et al, to have looked in the art for other specific active agents suitable for spray formulations of liquid carriers, as taught by Physicians' Desk Reference, with reasonable expectations of successfully preparing suitable formulations for various therapies. Furthermore it would have been obvious to one of ordinary skill in the art to have substituted any suitable active agent for the active agents of Fu et al's buccal spray formulations as taught by Physicians' Desk Reference. In other words, the claims would have been obvious because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims **1 and 22** are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 6,676,931. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are obvious over the reference claims. In other words, claims 1 and 22 are generic to all that is recited in claim 2 of U.S. Patent No. 6,676,931. Specifically, the method of administering a buccal spray composition comprising zolpidem and a polar solvent recited in claims of instant Application are obvious over the composition recited in claim 2 of U.S. Patent No. 6,676,931. In other words the method of administering the buccal spray formulations would have needed the buccal formulations of the reference claims. The active agent can be substituted.

Claims **1-8, 10, 22-26, 28, 40-46, 48, 57-59 and 61** are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,110,486. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are anticipated by the reference claims. In other words, claims 1-8, 10, 22-26, 28, 40-46, 48, 57-59 and 61 are generic to all that is recited in claims 1-9 of U.S. Patent No. 6,110,486. Specifically, method of administering a buccal spray composition comprising zolpidem and a polar solvent recited in claims of instant Application are anticipated by the composition recited in claims 1-9 of U.S. Patent No. 6,110,486.

Claims **1-8, 10, 22-26, 28, 40-46, 48, 57-59 and 61** are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 84-85, 2-7, 12, 19, 45, 50 and 57-59 of co-pending Application No. 10/230,085. The double patenting rejection is proper because the examined claims and the reference claims are substantially the same. The difference is that claims of the co-pending Application '059 recite a broader scope of active agents which includes hypnotics such as zolpidem. Thus the instant claims are anticipated by the reference claims.

This is a provisional obviousness-type double patenting rejection.

Claims **1-8, 10, 22-26, 28, 40-46, 48, 57-59 and 61** are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 27-34, 54-59 and 80-82 of co-pending Application No. 09/537,118. The double patenting rejection is proper because the examined claims and the reference claims are substantially the

same. The difference is that claims of the co-pending Application '118 recite a broader scope of active agents which includes hypnotics such as zolpidem. Thus the instant claims are anticipated by the reference claims.

This is a provisional obviousness-type double patenting rejection.

Claims **1-8, 10, 22-26, 28, 40-46, 48, 57-59 and 61** are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims of co-pending Application Nos. 10/230,060; 10/230,072; 10/230,059; 10/230,086; 10/230,080; 10/230,075; 10/230,073; 10/671,708; 10/671,709; 10/671,717; 10/671,720; 10/671,719; 10/671,710; 10/726,625; 10/726,585; 10/834,815; 10/663,817 and 10/928,997 in view of Swaminathan et al (WO 9733621). The double patenting rejection is proper because the examined claims are obvious over the reference claims. The difference between claims of the instant application and the claims of the reference applications is the active agents. For example, Application 10/230,075 recites active agents such as anti-arrhythmics, anti-hypertensives, heart regulators, vasodilators, etc. Application 10/230,059 recites active agents such as anti-opioids, anti-migraines, pain control agents, etc. Application 10/663,817 recites active agents such as sleep inducers, antivirals, antibiotics, antiasthmatics, antiemetics, etc. It is also noted that many such classes of active agents are common or overlap with the agents of the instant application. Swaminathan et al (WO 9733621) teaches that various active agents can be used in the said solvent system for administration. Thus it would have been obvious to one of ordinary skill in

the art to have substituted one active for the other in the same solvent system for the same method of administration.

This is a provisional obviousness-type double patenting rejection.

Pertinent Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

1) Oguri et al (JP 02-026661) teaches formulations for aerosol delivery comprising an active agent and a liquid carrier. Suitable active agents include analgesics and carrier formulations include polar and non-polar solvents and other agents. Carrier formulations may comprise a mixture of a polar and a non-polar solvent. Polar solvents include water, alcohols such as ethyl alcohol, propylene glycols. Non-polar solvents include hydrocarbons or halogenated hydrocarbons are suitable. Menthol is one of flavors used.

2) Kim (6,143,329) teaches aqueous-based pharmaceutical compositions comprising an active agent such as triamcinolone, purified water, Polysorbate and dextrose (see example 1). The said formulations are placed in a spray bottle for delivery to the surface of mucosa.

Response to Arguments

Applicant's arguments filed 10/30/07 have been fully considered but they are not persuasive.

Applicant argues that Deihl would not have been considered a credible or relevant teaching because "each spray is 50 microliters and contains 1 milligram of acetaminophen or

ibuprofen. This treatment is repeated once after five minutes. That is, Deihl teaches a total dose of 4-8 milligrams of acetaminophen or ibuprofen". Applicant however agrees that "Deihl purports to teach a sprayable analgesic composition where an analgesic is capable of being absorbed into bloodstream through the buccal mucosa" and that Deihl's compositions comprise acetaminophen or ibuprofen in an aqueous ethanol base. Applicant is arguing limitations not claimed. Claims are drawn to a method of **administering** a composition to the buccal mucosa by spraying the oral mucosa with the said compositions comprising various active agents such as anti-spasmodics, anti-diarrheals, anti-diuretics, agents for treating nausea, etc. The said compositions comprise the active agent in an amount between 0.001 and 60% and a polar solvent in an amount between 30 and 99.69% both by weight of the composition. The formulation exemplified by Deihl (example 1) comprises about 1.93% acetaminophen (an active agent) and about 51.87% of a polar solvent mixture such as ethanol and water. Thus Deihl is clearly teaching a composition comprising an active agent and the polar solvent in amounts that overlaps the required amounts in the instant claims. Deihl teaches and Applicant agrees, delivery of the said sprayable formulation to the oral mucosa for absorption through the buccal mucosa. Therefore, it is clearly shown that Diehl et al in combination with Kanios et al meet all the limitations.

Applicant's argument that Diehl does not teach a therapeutic amount is not persuasive because Deihl specifically compares oral dosages and buccal dosages and teaches that patients need less medicaments for buccal absorption than they would for oral (gastrointestinal) absorption. Diehl discloses that as little as $1/20^{th}$ of an oral dose of a medicament may be needed for buccal administration. Thus it is disclosed that Diehl's dosage is at a therapeutic level. Also

as stated above, the amounts disclosed in Diehl's example is within a concentration range claimed as "therapeutic amount" by Applicant. Thus the limitations are met.

Applicant argues that according to Remington, 19th ed. "when only small amounts of drugs are required to gain access to the blood, the buccal route may be satisfactory, providing the physicochemical prerequisites for absorption by this route are present in the drug and dosage form. Only a few drugs may be given successfully by this route". This is not persuasive. Various references e.g. Deihl, Fassberg and Cassidy et al, 1993, *Controlled buccal delivery of buprenorphine* (copy provided) have shown that many different active agents such as analgesics, polypeptides, antibiotics, etc, can successfully be administered to the buccal mucosa. Also there is no criticality disclosed by the Applicant in spraying the recited agents to the oral mucosa. In fact as seen in cited references and many co-pending applications, it is obvious that many different active agents can be included in the same formulation base and successfully sprayed in the oral mucosa. Therefore substituting different active agents in the same solvent formulation is an obvious variation and does not alter the scope of the claim.

Applicant argues that Fu et al teaches compositions for sublingual delivery of specific polypeptides and in the presence of a permeation enhancer. This is not persuasive because Fu teaches sublingual delivery of formulations comprising a therapeutic agent, particularly polypeptides. Also it is noted that instant formulations employ the open-ended language of "comprising" and do not exclude permeation enhancers. Thus presence or absence of the permeation enhancers is not relevant to the examination of instant claims here.

Declaration

Declaration of Dr. Frank Blondino has been fully considered. Applicant argues that Dr. Blondino's Declaration explains in detail, data from the studies showing that zolpidem oral spray demonstrated consistently faster drug absorption than the tablet and that a lower dose of zolpidem in an oral spray can be used to achieve the same blood level as a higher dose oral tablet.

While the Office agrees with Dr. Blondino's assertions and the Applicant's statement regarding the results of the clinical studies, neither the Declaration nor the arguments overcome the rejections. Declaration recites detailed results of studies comparing a spray dose of zolpidem with a tablet dosage form of zolpidem. The results show that the spray form typically has better pharmacokinetic profile as determined by Cmax and AUCs. In other words, there is no dispute that the buccal spray dosage from of a drug has a much better pharmacokinetic profile than its tablet or other oral dosage forms. It has been established that the spray forms (buccal, nasal or pulmonary) have a faster onset of action, eliminate the first pass effect, thus resulting in no or less side effects and a much lower amount of medicament is required to achieve the therapeutic effect. Diehl teaches and suggests that "It is highly advantageous to provide a composition for buccal absorption". Diehl states that "I have now discovered liquid analgesic compositions and methods of administering analgesic compounds which are conveniently and inexpensively prepared, conveniently administered, and which may provide the desired physiological effect at a lower total dose than that obtained by use of prior tabletted or swallowed liquid compositions".

Thus it has been clearly shown that instant claims would have been obvious over the references on record and that the Declaration fails to overcome the rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is 571-272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mina Haghighatian
Patent Examiner
December 28, 2007